

REVIEW

**on behalf of Prof. Dr. Nikolay Margaritov Runev, PhD,
Clinic of Propaedeutics of Internal Medicine "Prof. St. Kirkovich "-
University Alexandrovska Hospital, Medical University - Sofia**

Subject: dissertation on the topic:

"INVASIVE ASSESSMENT OF THE HEMODYNAMICS IN PATIENTS AFTER FONTAN OPERATION"

for the award of an educational and scientific degree "Doctor" in a professional direction 7.1. "Medicine", specialty "Pediatric Cardiology" in the field of higher education 7. "Healthcare and Sports" of Dr. Elisaveta Dimitrova Levunlieva, doctoral student of independent training in the Pediatric Cardiology Clinic at MHAT "NKB" EAD – Sofia.

Order No. 228/04.07.2022 of the Executive Director of MHAT "NKB" EAD for the appointment of a scientific jury.

Concise curriculum vitae:

Dr. Levunlieva graduated in "Medicine" at Medical University of Sofia in 1991. During the period 1991-2002 she worked as a physician in the Pediatric Ward of MHAT "Rahila Angelova" - Pernik and since 2002 hitherto she has been working in Pediatric Cardiology Clinic at MHAT "NKB". From 2004 to 2009 she was a part of the team of Pediatric Resuscitation and Intensive Care Ward.

Dr. Levunlieva has acquired specialties in: "Pediatrics" (1998) and "Pediatric Cardiology" (2006), and certificates in: "Interventional Cardiology" (since 2011) and "Echocardiography in childhood" (since 2014).

She is fluent in French, English and Russian - written and spoken.

She is a member of: Bulgarian Society of Cardiology, Bulgarian Society of Interventional Cardiology, Bulgarian Pediatric Association, Association for European Pediatric and Congenital Cardiology.

Dr. Levunlieva has 3 publications in foreign journals with IF, 13 articles published in our country in: "Bulgarian Cardiology", "Cardiovascular Diseases", "Pediatrics" and a total of 34 printed abstracts from participation in national and international symposia and congresses, of which 10 are in journals with IF.

The dissertation is written on 155 pages, of which 39 - literature review; 7 - purpose, tasks, material and methods; 35 - results, 27 - discussion; 3 - conclusions and contributions; 21 - applications, 13 pages - bibliography.

The dissertation is structured in the classical way with compliance of the proportions between its separate parts according to the generally accepted requirements in our country.

Relevance of the topic:

The topic of the dissertation is relevant both in theoretical and scientific-practical aspect. I have the following reasons for this statement:

1. The Fontan operation in patients with complex congenital heart diseases (CHD) with single-ventricle hemodynamics has a number of beneficial effects: separation of the systemic and venous circulation, volume unloading of the ventricle, oxygenation improvement, elimination of the risk of paradoxical emboli, significant improvement of survival and quality of life.
2. However, the Fontan operation has also its weaknesses: chronic venous and hepatic congestion, limited cardiac reserve at rest and during exercise, increased afterload, risk of arrhythmias and thromboembolism, need for reoperations.
3. Post-Fontan evolution and prognostic factors for early and late survival of the patients continue to be a subject of discussions and clinical trials.

Knowledge on the topic:

The review shows that the author is thoroughly acquainted with the available literature on the subject. I will mention only some of the main conclusions that emerge from the review:

1. The Fontan operation improves the prognosis in children with complex CHD, but the created non-physiological circulation is associated with an increased risk of multi-organ dysfunction. In the late period after the operation, manifestations of decompensation of the Fontan circulation are being observed: neuro-psychological, respiratory, endocrine, renal, hematological.
2. The cardiac catheterization is the only method for accurate measurement of the hemodynamic parameters after Fontan-operation and there are currently no generally accepted hemodynamic criteria for transcatheter closure of a fenestra (defenestration).
3. There is a lack of accurate data on whether and to what extent the administration of pulmonary vasodilators can have a beneficial effect on the hemodynamics: a decrease in pulmonary vascular resistance with an increase in pulmonary blood flow and ventricular preload, resp. cardiac output.

4. An evaluation of the long-term results after Fontan operation has not been done in our country, including invasive assessment of the hemodynamics in patients with complex CHD with single-ventricle physiology, operated in childhood.

Thus, the author fully justifies the idea of her study.

The formulation of the **purpose and tasks** follows the conclusions of the literature review.

The material and the methods give full grounds to believe in the obtained results.

A study on 71 children with complex CHD type single-ventricle has been conducted, of them 31 (43.7%) - girls and 40 (56.3%) - boys, with an average age of 4.48 ± 2.01 years, operated in Pediatric Cardiology Clinic at MHAT "NKB" during the period 2000-2020 and meeting the following inclusion criteria:

- ✓ CHD with single-ventricle hemodynamics and completed stages of physiological correction;
- ✓ type Fontan-operation – total cavo-pulmonary anastomosis with extracardiac conduit;
- ✓ patients who survived the early postoperative period;
- ✓ a follow-up after the surgery for at least 1 year;
- ✓ at least one postoperative catheterization;
- ✓ signed informed consent by the parents,
- ✓ age under 18 years.

The data have been obtained from the operative protocols, discharge letters and catheterization protocols (until 2009 – retrospectively, after 2010 cardiac catheterizations have been performed according to the Clinic protocol).

The studied children have been undergone preoperative and one or more postoperative invasive assessments with evaluation of hemodynamic parameters: systemic oxygen saturation (SatO₂), caval and pulmonary pressure, ventricular systolic and end-diastolic pressure, transpulmonary gradient, systemic arterial pressure, pulmonary and systemic blood flow, pulmonary and systemic vascular resistance.

The cardiac catheterization includes:

✓ manometry in superior and inferior venae cavae, both branches of the pulmonary artery, wedged pulmonary capillary pressure, left atrium (through the fenestra), systolic and end-diastolic pressure in the single ventricle, systemic pressure;

✓ oximetry from the both venae cavae to calculate the saturation in mixed venous blood, the both pulmonary arteries, left atrium and aorta.

In patients with a fenestra, the hemodynamic parameters have been compared before and after Fontan, before and after temporary balloon occlusion, and after definitive defenestration.

The following criteria have been used for definitive fenestration closure according to the Clinic protocol:

- ✓ increase in systemic SatO₂ over 90%;
- ✓ increase in cavo-pulmonary pressure by ≤ 4 mmHg from baseline (maximum up to 16 mmHg).
- ✓ SatO₂ decrease in mixed venous blood by $\leq 20\%$ of the baseline (or arterio-venous difference up to 30%);
- ✓ cardiac output reduction by less than 30% of baseline;
- ✓ systolic arterial pressure decrease by less than 15 mmHg from baseline;
- ✓ lack of debarrassing venous collaterals.

Modern statistical analysis of the results has been done using the statistical package SPSS 21.0. for Windows. The data for quantitative parameters are presented as mean \pm standard deviation, and for qualitative variables – as absolute values and relative frequencies (percentages). A test for normality of the distribution has been performed for quantitative variables using the Kolmogorov-Smirnov and Shapiro-Wilk methods. A Levene's test for equality of the variations has been applied. A t-test or Mann-Whitney test are used to compare one quantitative variable in two independent groups, according to the shape of the distribution. A test for statistically significant correlation has been done using Pearson's correlation coefficient in case of normal distribution of two quantitative variables. The diagnostic potential of the investigated parameters (sensitivity-specificity ratio) are determined by ROC analysis with an assessment of the area under the ROC curve. The critical level of significance used is $\alpha = 0.05$, with the corresponding null hypothesis rejected at P-value $< \alpha$.

Characteristics of the results and the discussion:

The most important results in my opinion are the following:

1. After Fontan operation with an extracardiac conduit in patients with complex CHD of single-ventricle type, the following beneficial effects are established:

- ✓ increase in the oxygen saturation;
- ✓ increase in the pulmonary/systemic blood flow ratio (Qp/Qs);
- ✓ reduction of the ventricular end-diastolic pressure (EDP) in the absence of significant changes in pulmonary vascular resistance, cavo-pulmonary pressure and systemic blood flow.

2. Morphologically, the left single-ventricle type has more favorable hemodynamic characteristics at the last postoperative invasive assessment: significantly lower ventricular EDP and higher Qp/Qs ratio.

3. In the long-term postoperative evolution, an increase in the transpulmonary gradient has been found.

4. The fenestration favors early postoperative adaptation, but results in significant hypoxia in the late postoperative period. The precise hemodynamic assessment during test occlusion allows, on the basis of clearly defined criteria, to select the patients in whom the defenestration will have a beneficial effect with a significant increase in oxygen saturation.

5. The selective pulmonary vasodilators significantly decrease the pulmonary vascular resistance (a major factor for unfavourable postoperative evolution) and cavo-pulmonary pressure, improving transpulmonary blood flow and systemic SatO₂.

The results are appropriately illustrated with 57 tables and 39 figures.

I agree with the report on the conclusions and contributions of the dissertation.

There are 297 cited publications in the bibliography, of which 11 are in Cyrillic and 80 - since the last 5 years.

Conclusion:

The dissertation work has a clearly set purpose and specific tasks for its achievement. It is clear that Dr. Levunlieva has a very good knowledge of the statistical methods for scientific information processing, is able to interpret the obtained research data and reaches logical conclusions.

The dissertation contains scientific and scientific-applied results, which represent an original contribution and meet the requirements for awarding the educational and scientific degree "Doctor".

Among them, the following are especially valuable in my opinion:

(1) The systematic analysis of the invasively assessed hemodynamic parameters in patients with a functionally single-ventricle heart and completed stages of Fontan-palliation, performed for the first time in our country.

(2) The evaluation of the prognosis after Fontan operation with an extracardiac conduit using a scoring system based on the hemodynamic catheterization data, which shows high sensitivity and specificity in patients with completed stages of Fontan palliation.

(3) The established protocol for follow-up and hemodynamic invasive evaluation of patients with single-ventricle type CHD after completion of the stages of Fontan-type functional correction.

This gives me grounds **to vote in favor** of the award of an educational and scientific degree "Doctor" in the specialty "Pediatric Cardiology" to Dr. Elisaveta Dimitrova Levunlieva, a doctoral student of independent training in the Pediatric Cardiology Clinic at MHAT "NKB" EAD - Sofia.

12.09.2022

Signature:



Prof. Nikolay Runev, PhD